ALKYLATIONS BY REPLACEMENT OF AMINO GROUPS: STUDIES OF THE MECHANISM OF THE REACTION

BY

JAMES HENRY BREWSTER

A. B., Cornell University, 1942

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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Introduction

The alkyl ester of a strong acid can react with a tertiary amine to form a quaternary ammonium salt. Such a salt can decompose to form a tertiary amine and either an olefin or an organic derivative of the anion of the salt (1).

The olefin-forming reaction of quaternary salts has been used extensively in alkaloid structure studies, and has also been applied in synthesis. The synthetic value of the anion-alkylation reaction has only recently been realized.

Amines prepared by the Mannich reaction (2) contain labile amino groups which can readily be eliminated or be replaced by anionic radicals. It seemed desirable to attempt to correlate the "labile amine" reactions of "Mannich bases" with the corresponding reactions of quarternary ammonium compounds on the basis of current electronic theories of reaction mechanism.

Discussion of Results

The Mannich bases of acetophenone (3) and β-naphthol (4) react with secondary amines by amine exchange. Salts of the ketonic Mannich bases react only a little more readily than the tertiary amine. Optically active 1-α-piperidinylbenzyl-2-naphthol (5) reacted with piperidine to form only racemic 1-α-piperidinylbenzyl-2-naphthol.

Mannich bases of β-naphthol can suffer replacement of the amino group by cyanide ion (6); complete hydrolysis of the nitrile occurs during the reaction. An important side reaction is the formation of di-(2-hydroxyl-1-naphthalene)-methane, a reaction which also occurs when the naphthol

Mannich base is heated with dilute alkali (7) or in xylene.

Isobutyrophenone condenses with formaldehyde and dimethylamine under "forcing conditions" to form the hydrochloride of dimethylaminapivalophenone. This Mannich base could undergo amine replacements only by way of a carbonium ion formed by unimolecular decomposition of one of its salts. Such replacements do not occur with the amine, its hydrochloride or its methiodide, for other reactions seem to take place more readily. The tertiary amine is stable to strong base, but undergoes the reverse Mannich reaction in weakly basic or acidic medium. The quaternary salt reacts with strong alkali to form benzoic acid.

The methyl ether of α-dimethylaminomethyl-β-napththol could not be prepared by methylation of the naphthol Mannich base, nor by the Mannich reaction with β-naphthyl methyl ether as the active hydrogen compound. It was prepared indirectly by way of the acid-catalyzed condensation of N-methylol benzamide with β-naphthyl methyl ether; the benzamido compound was hydrolyzed by strong alkali and the primary amine so formed was methylated by means of formaldehyde and formic acid.

This tertiary amine was non-reactive in amine exchange reactions and in cyanide and malonate alkylations. It did not form a diarylmethane but was stable to heat and alkali. The quarternary salt underwent amine replacements with piperidine, sodium cyanide and sodio-malonic ester.

The Mannich reaction can occur with compounds containing only one active hydrogen atom. It does not necessarily require hydroxymethylation of the active hydrogen compound, but probably occurs by direct aminomethylation. Further evidence for this point of view was found in the failure of saligenin to react with morpholine under conditions which permit phenol, formaldehyde and morpholine to condense in high yield.

It was found that the methiodide of optically active N,N-dimethyl-α-phenylethylamine suffers amine replacement by acetate with complete inversion of configuration. Styrene and dimethyl-α-phenylethylamine are also formed in this reaction.

Alkylation of malonic ester with this optically active quarternary salt resulted in the formation of racemic α-methylbenzylmalonic ester and largely racemized dimethyl-α-phenylethylamine. This indicates that some racemization of the quaternary salt occurs prior to other reactions.

On theoretical grounds it would be expected that Mannich bases would suffer amine replacement reactions by SN1 mechanisms more readily than by SN2 mechanisms. While mechanisms involving preliminary amine elimination (E1 or E2) are not necessary to amine replacement reactions of quaternary salts, only compounds capable of such elimination reactions have a high order of activity as alkylating agents.

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VITA

The author was born in Fort Collins, Colorado, on August 21, 1922. He attended the public schools of Casper, Wyoming, Kansas City, Missouri, and Litchfield, Connecticut, and was graduated from Litchfield Public High School in June, 1938. After a year's study at the Storm King School, Cornwall-on-Hudson, New York, he entered Cornell University, from which institution he received the degree of Bachelor of Arts in June, 1942. He was employed by the Atlantic Refining Company, Philadelphia, Pennsylvania, until, in August, 1943, he joined the American Field Service. He served as an ambulance driver with units of the British, Canadian, New Zealand, Indian and Italian armies, as well as with a partisan group, in the Eighth Army sectors in Italy; he was discharged in November, 1945. In March, 1946, he entered the Graduate College of the University of Illinois, where he held a part-time teaching assistantship until September, 1947, and a University Fellowship during the academic year 1947-1948.

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